FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

Date: November 15, 2007

From: Lori Tull, Regulatory Management Staff, OCTGT, HFM – 705

To: The file, STN 125197/0

Subject: Type C BLA Teleconference - CMC discussion summary

Teleconference Date: October 16, 2007 **Time:** 1-2:30

Location: Woodmont Office Complex 1/ Conference Room 200S

Meeting Requestor/Sponsor: Dendreon Corporation

Product: Sipuleucel-T

Proposed Use: Treatment of men with asymptomatic metastatic androgen independent prostate cancer.

Type of meeting: Other BLA - CMC discussion

Date draft Faxed to Sponsor: October 16, 2007

Meeting Objectives: This meeting was requested to discuss in detail the CMC-related deficiencies noted in the May 8, 2007 FDA Complete Response Letter regarding BLA STN 125197/0 for sipuleucel-T.

Sponsor questions and FDA response:

1. In the May 8, 2007 complete response letter (Attachment 1), item #1 stated that outstanding issues from the pre-license inspection have yet to be resolved.

a) Dendreon has provided responses to the pre-license inspection observations in 2 submissions: the March 2, 2007 response to FDA Form 483, Attachment 2, and the April 20, 2007 Amendment 009 to BLA 125197/0. All 483 commitments communicated in the March 2007 response have been successfully executed according to the proposed timeline. (The expansion of (b)(4) is on schedule for October 2007.) Can the Agency please confirm that these responses are sufficient to address the 483 observations? In addition, we are requesting a copy

of the Establishment Inspection Report for the February 2007 pre-license inspection.

FDA Response

1) For inspection item #3 regarding the QC laboratory we ask that you respond to the following remaining issues:

   a) Please provide a copy of FRM-60334 and describe in greater detail how this is generated from electronic document management.

   b) Please describe how the barcode is inserted into the (b)(4) software and who is responsible for ensuring it has the correct barcode. Is the (b)(4) software and the [redacted] software linked in any way, or are their other safety measures in place, so that if a sample or form is submitted with the wrong barcode (according to the [redacted] software) to the QC lab that the discrepancy will be immediately noticed by the [redacted] software?

   c) Please clarify how many barcode readers will be in place in the QC lab and where the bar code reader(s) be located.

   d) Please revise SOP-10400 (2/9/07) to include barcode scanning within the QC lab.

   e) How will the barcode system be validated and when is this expected to occur? How was the (b)(4) formula validated for generating the barcode (as stated in BLA amendment 009?

   f) Please clarify if test tube racks can hold multiple samples from different lots and if there is any plan to label racks.

   g) Please clarify how QC samples and production lots will be prioritized.

   - Dendreon responded that these issues could be addressed offline.

2) CBER understands the importance of the EIR and will send Dendreon a copy as soon as possible.

b) In response to item #1, Dendreon committed to qualifying the concurrent use of (b)(4) production modules in the New Jersey facility at full capacity. We intend to provide data from the qualification with our response to the May 8, 2007 letter. Does the Agency agree that the proposed qualification study (refer

to Section 3.0) will be sufficient to support licensure for production of up to [redacted] lots of sipuleucel-T?

FDA Response

1) Your Process Capacity Qualification study indicates that you could process [redacted] lots for [redacted] in Module [redacted] at the conditions specified in your protocol. However, this study did not cover the actual manufacturing process in which the harvest of Day [redacted] samples from the [redacted] run overlaps with the process of Day [redacted] samples from the [redacted] run, both with [redacted] lots. The current qualification study did not demonstrate that you could [redacted] manufacture [redacted] lots within the specific time frame.

2) Similarly, we have concerns with your proposed [redacted] workstation capacity qualification study with [redacted] t lots for [redacted] modules. The proposed study design with only [redacted] of [redacted] lots does not cover the overlapping time between processing of the [redacted] Day [redacted] samples from the previous run and the [redacted] Day [redacted] samples from the subsequent run.

3) The environmental monitoring (EM) data for the Process Capacity Qualification study were not provided. Please provide the EM data including personnel monitoring for your validation study.

   - Dendreon responded that they would submit this information.

[redacted] For your capacity qualification study, we recommend that you consider shipping the processed samples to specified destinations to ensure that multiple samples can be delivered within the [redacted] hour shelf life time frame.

   [redacted] Dendreon responded that they would consider the recommendation, and commented that they might be able to address this issue with data from the clinical experience.

5) FDA would like clarification on whether you will apply for licensure for a capacity of [redacted] lots or [redacted] t lots for this BLA? If you plan to apply for [redacted] lots please provide information on when you will perform the qualification studies.

   - Dendreon responded that their current proposal was for QC testing of [redacted] lots at the same time and [redacted] product lots at the same time. FDA replied that there was a concern about how multiple samples coming in around the clock would be handled. Following more discussion, Dendreon stated that they may plan a proposal representing a snapshot of manufacturing. Dendreon also stated that they have made [redacted] lots total in the NJ facility (up to [redacted]) that provides additional practical experience. Data from these manufactured lots will be provided. They will withdraw the current proposal and plan on submitting a new proposal within the next four weeks.

c) At the April 4, 2007 teleconference, Dendreon and FDA discussed the use of the [redacted] production modules for [redacted] clinical and commercial manufacturing. Dendreon proposed that clinical and commercial manufacturing be segregated by campaigning, rather than by identifying [redacted] to be used exclusively for commercial manufacturing. The question was readdressed at the April 23, 2007 teleconference, where the Agency agreed to Dendreon's proposal. Can the Agency please confirm that they have no issues with Dendreon's proposal to use the modules on a campaigned basis, [redacted] to clinical and [redacted] to commercial manufacturing?

FDA Response

We are not able to provide an accurate answer to this question until we clarify what you mean by a campaign. Please clarify if any module will be used to manufacture commercial and clinical lots [redacted]. Are both commercial and clinical lots going to be [redacted] Are both commercial and clinical lots going to be received and shipped in the same receiving and packaging rooms at the same time? What procedural controls do you have to prevent mix-up of commercial and clinical lots during the production?

- Dendreon clarified that they were proposing that the clinical and commercial production would be [redacted]. Dendreon will provide the information to the BLA.

2. ***In response to item #2, Dendreon plans to provide additional information on the design and execution of the studies that support the stability of the [redacted]. Test data from the experimental lots presented in Figure 8 (BLA Section 3.2.P.2.3) will be provided for comparison with ranges of similar data observed during sipuleucel-T Phase 3 clinical experience. Does the Agency agree that the additional explanation and test data would adequately address this question?***

FDA Response

As long as the rationale for the testing procedure and study design is adequately explained and reasonable, and the additional test data from these lots demonstrate that they are representative of typical lots produced while under IND, this should adequately address this issue. Because the data in Fig 8 show that some lots may have recoveries as low as approximately [redacted] please include in your response the potential impact such a yield might have on meeting lot release criteria.

3. Item #3 in the May 8, 2007 letter requested additional data related to the validation of the shipping container and temperature of the final product during shipment at high external temperature. Data from sipuleucel-T stability studies, from the studies conducted to validate the shipper at 2 to 8°C, and from the study of shipped product, when taken together, demonstrate that product quality is maintained during shipment. (Refer to Section 4.0. Refer also to Question 4a below, describing additional stability studies.) Does the Agency agree that additional shipping validation studies would be redundant?

FDA Response

While we do not agree that additional shipping studies would be redundant due to the limited shipping studies conducted with actual product and the degree of robustness of the tests, a second validation study may not be necessary. This deficiency could also be addressed through additional real-time temperature monitoring. For example you could include temperature monitors in the shipping container for an agreed upon number of lots during the first 12 months of manufacturing as part of a post-marketing commitment.

- Dendreon responded that they are not aware of any temperature monitoring technology that would be suitable in this case. Dendreon proposed to design a study conducted over the course of a year to a variety of sites with simulated product. FDA responded that the simulated product would have to be close to the actual product. FDA's concern is the broad range of cool down times for the product. FDA recommended that Dendreon submit a proposal and justification.

4. Regarding the requirement for supporting data on shipping stability, as stated in item #4, Dendreon has the following questions:

a) Dendreon intends to conduct a stability study to evaluate the effect of exposure of sipuleucel-T to [redacted] temperature (an accelerated condition for a refrigerated product) such as might occur during product manufacturing, from addition of [redacted (b)(4)]. (Refer to Section 4.1.1.) The data generated from this study (and possible follow-on studies) will be used to determine whether Dendreon needs to establish time limits around these manufacturing steps. Does the Agency concur?

FDA Response

Yes, the additional data from the [redacted (b)(4)] temperature stability study would better simulate what the product is likely to encounter, and should provide the missing information.

b) Dendreon will submit shipping data from sipuleucel-T lots manufactured at the NJ facility. Existing clinical shipping data will be supplemented by a table of

modeled shipping logistics to illustrate shipping times from the NJ facility to various US locations using the planned transportation routes. (Refer to Section 5.0.) Does the Agency agree that these data will be sufficient to demonstrate the feasibility of shipping sipuleucel-T from the NJ facility and infusing it within the 18-hour shelf life as requested in item #4b?

FDA Response

The data provided in Section 5 address the question of whether the product can be shipped to expected destinations within the 18 hour shelf life with a reasonable remaining shelf life to be administered to the patient. However, we have the following comments:

a) Shipments of final product to infusion sites were in general scheduled to ship early in the morning. While we recognize that the variable [redacted] time allows for some flexibility in determining outbound shipping times, it would appear that APH units arriving late in the day would be difficult to ship early in the morning of Day (b)(4) processing. During inspection inspectors were told that APH and final product would be shipped at all hours of the day. Please clarify what times of day you expect to ship the final product, and if shipped later in the day how that might affect product shipping times.

- Dendreon requested clarification of this comment. FDA responded that early morning shipments may not reflect what would occur during full capacity manufacturing, i.e., Dendreon may have to ship at other times during the day. Dendreon replied that shipment times for the product are restricted by the need to deliver to infusion sites during normal business hours. Dendreon further stated they could provide an example of the scheduling from the clinical experience from product produced at the New Jersey facility.

b) Some routes were listed as a combination of air/ground and some as ground. Please comment on how well the shipping and stability studies reflect an all ground shipping route.

c) Please provide more information on how weather or other transportation delays would be compensated for those lots with long natural transport times.

- Dendreon responded that in almost every case they could make adjustments and still ship on time. The provided information includes at least two different routes for most destinations, and the actual route for shipping product would depend on traffic and weather conditions.

d) The simulation provided does not adequately address logistical issues that will be encountered when manufacturing at full capacity. We ask that you provide a similar simulation summary for coordinated lots manufactured at the scale of (b)(4)

incoming and (b)(4) outgoing lots per day, including an estimate for when QC testing would be initiated and completed. Simulations of one week of manufacturing should be provided. Such a simulation may not be necessary depending upon how robust a study they conduct in response to item #1.

5. Regarding the comparability of Phase 3 clinical product manufactured at sites other than Seattle and New Jersey (item #5), additional data will be provided for the 4 additional manufacturing sites used for Phase 3 clinical trials. Dendreon plans to analyze the site-specific data in the same statistical model used for the Seattle/New Jersey comparability analyses. In addition to showing the total number of lots manufactured at each site, Dendreon will provide tables of final product analytical data (similar to those provided in BLA section 3.2.S.4.4) where the manufacturing site is identified for each lot. Does the Agency agree that this response will satisfy the request in item #5?

FDA Response

Yes. Assuming that the data demonstrate comparability between the different manufacturing sites, this would be adequate.

6. In response to item #6:

a) The study dates, location, and instrument model used for the sterility method validation will be provided. Dendreon will also provide extensive information received from the (b)(4) manufacturer, , describing the similarities and differences between the (b)(4) and the (b)(4). (Refer to Attachment 3.)

b) Studies of environmental isolates obtained from the NJ facility are on-going and data will be provided with our response to the May 8, 2007 complete response letter.

c) The (b)(4) method is not being used for (b)(4) final release sterility testing. If we elect to use the (b)(4) method for any aspect of (b)(4) production in the future, we will first perform bacteriostasis/fungistasis studies and make the results available for review, as appropriate.

Will these submissions be sufficient for item #6?

FDA Response

It appears that the additional information will be adequate.

7. For the analytical method validation questions, as posed in item #7, the requested data for each method will be provided with our response to the May 8, 2007 complete response letter. Does the Agency agree that such data will suffice?

FDA Response

In addition to the requested data, it may be necessary to modify the appropriate SOPs to be consistent with the outcomes of the additional studies.

Please submit all submissions, in triplicate, to:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center, HFM-99, Suite 200N
1401 Rockville Pike
Rockville, MD 20852-1448
Attn: OCTGT/RMS

If you have any questions, please contact the Regulatory Project Manager, Lori Tull, at (301) 827-5102.

Attachments/Handouts:

FDA Attendees:

Stephanie Simek, Ph.D., Office of Cellular, Tissue and Gene Therapies
Kimberly Benton, Ph.D., Division of Cellular and Gene Therapies
Keith Wonnacott, Ph.D., Division of Cellular and Gene Therapies
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Dendreon Attendees:

Mary Coon Vice President, Quality
Heidi Hagen Vice President, Supply Operations
Mike Hartley Manager, Validation
Mike Poor Director, Supply Operations

Cyril Possa Director, QA Compliance and Validation
Nicole Provost Vice President, Product Development
Georgeta Puscalau Director, Quality Control
Elizabeth Smith Vice President, Regulatory Affairs
Connie Spooner Sr. Manager, Regulatory Affairs
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OCTGT/IOD/L.Tull:10/22/07
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